Editorial

〔Lab Med Int 2024; 3(3): 59-60〕

Extracellular vesicles control both coagulation and fibrinolysis to promote deep venous thrombosis

*Munekazu Yamakuchi, MD, PhD**

* Department of Laboratory and Vascular Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8544, Japan. E-mail: munekazu@m.kufm.kagoshima-u.ac.jp

See article volume 3(3): 95-107

Venous thromboembolism (VTE) is a disease concept that combines deep venous thrombosis (DVT) and pulmonary embolism (PE). Various pathological conditions can cause DVT, which is generated by Virchow's triad: stasis of blood flow, damage to vascular endothelial cells, and hypercoagulable states[1]. Although DVT is primarily characterized by swelling and pain in the lower extremities, many cases are asymptomatic, which can lead to PE and sudden death; therefore, prompt and accurate diagnosis is required. However, no clear diagnostic biomarkers are available for diagnosis. Echocardiography is suitable for identifying thrombi, and D-dimer is the most commonly used blood test. Although D-dimer levels within the reference range have diagnostic value as a rule-out test, even a high value has low disease specificity[2]. What are the alternative biomarkers for D-dimer levels?

Shiotsu et al. focused on large extracellular vesicles (LEVs) in blood to answer this question. Extracellular vesicles (EVs) are lipid bilayer membrane vesicles that encapsulate functional molecules such as proteins and nucleic acids and are secreted in various sizes. The minimal information for studies of extracellular vesicles 2018 (MISEV 2018) recommended referring to EVs separately according to their size and density, such as medium/large EVs (m/lEV) and small EVs (sEV); however, their functional differences are not well understood[3]. They included 28 patients with DVT, most of whom had carcinoma. In cancer-associated thrombosis, EVs derived from cancer cells promote thrombogenesis[4]. This is mainly due to the enhancement of the coagulation system by tissue factor on the EV membrane surface and promotion of platelet aggregation by podoplanin on the membrane[5]. They found that CD31 and CD61 positive LEVs, which are considered platelet-derived, increased in patients with DVT.

One important aspect of the study by Shiotsu et al. is that not only the membrane component of LEV, but also miR-4485, which is contained in LEV, was significantly increased in DVT patients. Receiver operating characteristic analysis indicates that miR-4485 could be a potential biomarker for DVT. Although various DVT-related miRNAs have been proposed[6], new miRNAs can be added to the list. Another important aspect was the identification of tissue plasminogen activator (tPA) as a target gene of miR-4485. LEVs from patients with DVT suppressed tPA expression in human umbilical vein endothelial cells (HUVECs). tPA is secreted from the Weibel-Palade bodies of endothelial cells and is present in the blood, mostly in complex with its specific inhibitor, plasminogen activator inhibitor 1 (PAI-1). tPA converts plasminogen into plasmin and initiates fibrinolytic reactions. Therefore, miR-4485 may promote DVT by decreasing tPA levels and delaying the fibrinolytic reaction. They found that LEV containing miR-4485 must be platelet-derived, indicating a novel phenomenon in which platelets regulate the fibrinolytic system.

Several points need to be addressed. First, platelet-derived LEVs increase in patients with DVT due to thrombus formation and platelet activation, and can this be a predictor of DVT, changes in this miRNA as DVT progresses, and whether the number of LEVs correlate with the degree of DVT are unknown. Second, although miR-4485 in LEVs is endocytosed by endothelial cells and inhibits tPA expression, in vivo data are required to demonstrate that the prothrombotic effects of LEVs are mediated by miR-4485. Furthermore, miR-4485 may have many other target genes besides tPA, and a comprehensive evaluation of the miRNAs encapsulated in LEVs is required based on the results of a comprehensive analysis of these genes. Finally, could the regulation of LEVs

or miR-4485 be a therapeutic target? As described, the increase in miR-4485 in platelets and endothelial cells appears to be associated with mitochondrial function; however, the underlying mechanism has not been elucidated. Although further studies are needed, this study reveals a novel role for platelet-derived LEVs in the pathogenesis of DVT and is a valuable clue for future research.

References

1) Stone J, Hangge P, Albadawi H, et al. Deep vein thrombosis: pathogenesis, diagnosis, and medical management. Cardiovasc Diagn Ther. 2017 ; 7:S276-S84. doi: 10.21037/cdt.2017.09.01.

2) Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. Blood Adv. 2018 ; 2:3226-56. doi: 10.1182/bloodadvances.2018024828.

3) Thery C, Witwer KW, Aikawa E, et al. Andriantsitohaina R, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. J Extracell Vesicles. 2018 ; 7:1535750. doi: 10.1080/20013078.2018.1535750.

4) Tatsumi K. The pathogenesis of cancer-associted thrombosis. Int J Hematol. 2024 ; 119:495-504. doi: 10.1007/s12185-024-03735-x.

5) Hisada Y, Mackman N. Cancer-associated pathways and biomarkers of venous thrombosis. Blood. 2017 ; 130:1499-506. doi: 10.1182/blood-2017-03-743211.

6) Fang C, Huang F, Yao M, et al. Advances in microRNA regulation of deep vein thrombosis through venous vascular endothelial cells (Review). Mol Med Rep. 2024; 29: doi: 10.3892/mmr.2024.13220.